PSJ2 Exh 101

Risk Management (REMS) for Tapentadol ER

CHAPTER 1:
Potential Risks Associated With Opioids and Tapentadol ER

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CHAPTER 1: POTENTIAL RISKS ASSOCIATED WITH OPIOIDS AND TAPENTADOL ER

LEARNING OBJECTIVES

Upon completion of this chapter you will be able to:

- Identify the potential risks associated with opioid therapy
- Explain why respiratory depression is one of the most serious risks of opioid therapy
- Differentiate between misuse, abuse, diversion, tolerance, and dependence
- Discuss the rationale behind the FDA's class-wide Risk Evaluation and Mitigation Strategies (REMS) for opioid medications
- Discuss why the potential for drug-seeking behavior should be assessed prior to and during opioid therapy
- Describe assessment tools that are available for opioid risk assessment
- Describe the components of FDA-approved REMS for OxyContin®, Embeda®, and Exalgo®
- Discuss the importance of proper patient and dose selection for opioid medications

Risk Management (REMS) for Tapentadol ER

OVERVIEW

Risk Evaluation and Mitigation Strategies (REMS) are risk management programs that are mandated by the Food and Drug Administration (FDA), and that may be required for any drug, pre- or postmarketing, to ensure the benefits of the drug outweigh the risks associated with its use.[1]

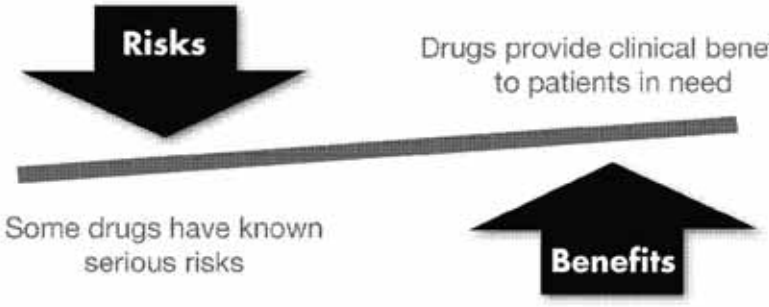
The FDA was granted the authority to require REMS programs under Title IX of the Food and Drug Administration Amendments Act (FDAAA) of 2007.[2] This act, which went into effect March 25, 2008, granted the FDA the power to manage drug risks more aggressively.[3] For example, the legislation granted the FDA the authority to require REMS as well as the ability to enforce them. The FDA may impose civil monetary penalties, declare a drug misbranded, and restrict interstate commerce if the requirements of the REMS are not met.[2]

Making the Link

It is important for you to have a basic understanding of the REMS, since product approval and continued availability of a drug are directly linked with its REMS program. These FDA-mandated programs, like a Black Box Warning or Contraindications, are designed to mitigate serious risks associated with a drug.[1,2] You will need to communicate the importance of the REMS in your discussions with healthcare professionals. If a healthcare professional has a question regarding the REMS program, you should direct them to contact the Company-specific Call Center for additional information

The goal of a REMS, ensuring the benefits of a drug outweigh its risks, is in keeping with the Johnson & Johnson Credo, which begins, "We believe our first responsibility is to the doctors, nurses and patients, to mothers and fathers and all others who use our products and services..." The Johnson & Johnson credo may be read in its entirety at: *http://www.jnj.com/wps/wcm/connect/c7933f004f5563df9e22be1bb31559c7/our-credo.pdf?MOD=AJPERES.*[4]

Figure 1. Goal of REMS[1]



Managing the patient and public safety risks associated with a pharmaceutical product is an important component of the highly-regulated processes of drug development, approval, and marketing. The FDA oversees these processes by[1]:

- Premarket evaluation of drug safety and effectiveness
- Ensuring that product labeling is appropriate
- Monitoring drug-related advertising and promotion
- Overseeing adverse event monitoring and reporting[1]

These processes are sufficient for mitigating the risk and preserving benefits for the majority of approved products.[2] Those products with risks that can not be adequately addressed through routine processes may be required to have a REMS.[1]

When the FDA determines a REMS is necessary to ensure the benefits of a drug outweigh the risks associated with it, it also determines what elements of the REMS must be included.[2] The elements of a REMS may include development of a Medication Guide or a Patient Package Insert, a Communication Plan, Elements to Assure Safe Use (ETASU), an Implementation System (for the ETASU).[2] REMS are required to include a Timetable for Assessment of the REMS, which specifies when an assessment of the REMS program will be submitted to the FDA. These mandatory assessments evaluate the efficacy of all the elements of the REMS program and recommend modifications to the goals, objectives, or elements of the REMS program, if needed.[2]

Additionally, the elements required for each REMS may vary based on the drug and the risks associated with it.[2] Drugs with a lower risk might require only a Timetable for Assessment and a Medication Guide—a document written specifically for the patient to provide important information about a drug.[2] On the other hand, some drugs with significant known risks would not be marketable without specific steps being taken to mitigate those risks; the REMS for these drugs would include ETASUs, and might require an Implementation System to monitor and evaluate the implementation of the REMS.[2]

Figure 2. The Components of a REMS[2]

Element	Example
Timetable for Assessment *(required)*	Minimum FDA requirement 18 months, 3 years, and 7 years after REMS approval
Medication Guide/PPI *(potential)*	Education tool provided to each patient when the drug is prescribed/dispensed
Communication Plan *(potential)*	For example, letters to healthcare providers, communications to professional societies, professional education
Elements to Assure Safe Use (ETASU) *(potential)*	Special requirements or restrictions to optimize safe use of products
Implementation System *(potential)*	System to monitor, evaluate, and improve Elements to Assure Safe Use

To date, FDA has approved more than 180 drugs with REMS, including several medications manufactured by Johnson & Johnson or their subsidiaries.[5] Approximately 100 REMS were approved as of early 2010; the majority of these required only a timetable for assessment of the REMS and a medication guide (~70%). Approximately 19% of the REMS approved by early 2010 required the implementation of a communication plan, while approximately 10% required elements to assure safe use.[6] Some Johnson & Johnson products, and the required elements for each REMS, are shown in Table 1. Notice that NUCYNTA®, an immediate-release form of tapentadol, requires a REMS.

Risk Management (REMS) for Tapentadol ER

Table 1. North America Pharmaceutical Risk Evaluation and Mitigation Strategies (REMS)[5,7]

Drug	REMS Approval Date	Timetable for Assessment	MG	Communication Plan	ETASU	Implementation Plan
NUCYNTA®	11/20/08	✓	✓			
Topamax®	4/23/09	✓	✓			
Simponi®	4/24/09 Released from REMS requirement 3/17/11					
Levaquin®	4/27/09	✓	✓			
Stelara®	9/25/09 10/20/10 (last modified)	✓	✓	✓		
Procrit® (non-oncology)	2/16/10	✓	✓	✓		
Procrit® (oncology)	2/16/10	✓	✓	✓	✓	✓
Pancreaze®	4/12/10	✓	✓			
Regranex®	4/28/10	✓	✓			

MG = Medicine Guide

ETASU = Elements to Assure Safe Use

Making the Link

The tapentadol ER REMS is designed to educate healthcare professionals on the risks of misuse, abuse, and overdose that are associated with the use of opioid medications. It will also educate healthcare professionals in risk assessment and identification of drug-seeking behavior. The REMS program is also designed to educate healthcare providers on the need to counsel patients to keep tapentadol ER out of the reach of children, and the importance of encouraging patients to read the Medication Guide they will receive with each filled prescription of tapentadol ER.[8]

The REMS for tapentadol ER will be discussed in more detail in Chapter 2 of this module. In Chapter 2, we will review the potential risks associated with **opioid** drugs and with tapentadol ER in particular. Chapter 1 will briefly discuss the components that will be included in the class-wide REMS for opioid medications. Chapter 1 will also examine some currently-approved examples of REMS for other opioid medications.

opioid: a term originally used to denote synthetic narcotics resembling opiates but increasingly used to refer to both opiates and synthetic narcotics

Respiratory Depression

One of the most serious risks associated with the use of tapentadol ER, and with all opioid drugs, is the risk for **respiratory depression**. Although respiratory depression is not a common adverse effect of opioid medications, it is potentially fatal.[9]

respiratory depression: ventilation that fails to provide adequate oxygen to the cells and to remove excess carbon dioxide from them

Most medically used opioid drugs achieve analgesia by acting as **mu-opioid receptor (MOR) agonists**. Mu-opioid receptor agonists act at various levels in the pain pathway to inhibit the transmission of the pain signal and pain realization.[10]

mu-opioid receptors: receptors responsible for initiating a signaling cascade that mediates the actions of many hormones and neurotransmitters[9]

Mu-opioid receptors are involved with a variety of physiologic effects, including respiratory control; therefore, mu-opioid receptors are abundant in the respiratory centers of the **brainstem**.[9] Drug-induced inhibition of the opioid receptors in these control centers may result in respiratory depression.[11]

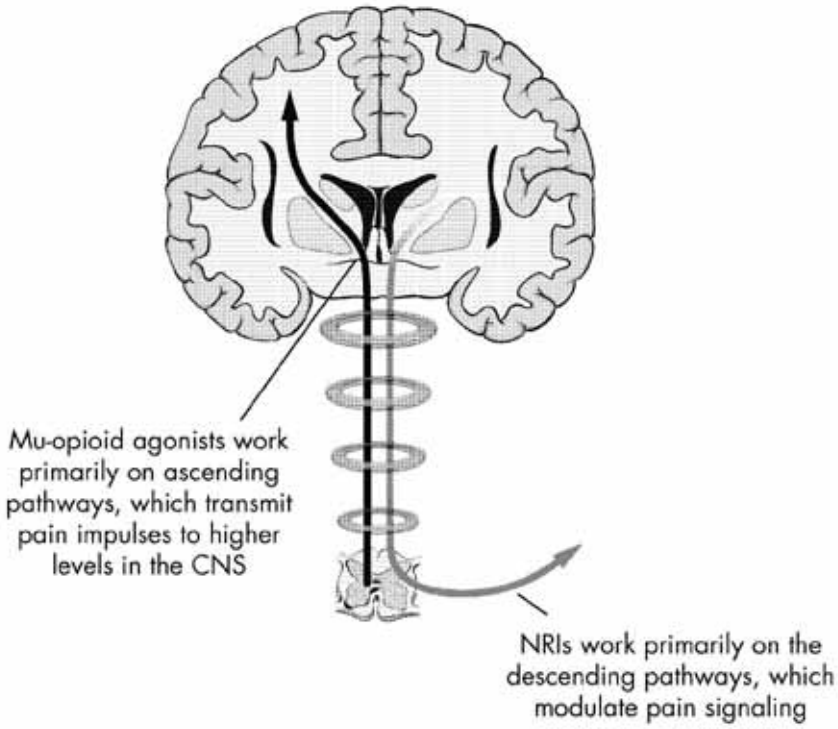
agonist: a drug that binds to a receptor and stimulates its function

brainstem: the part of the brain closest to the spinal cord that controls involuntary functions, such as breathing and heart rate

Tapentadol, the active ingredient in tapentadol ER, has a dual mechanism of action; it is believed to act both as a mu-opioid receptor agonist and as a **noradrenaline reuptake inhibitor**, which potentiates the effect of opioids.[12]

noradrenaline reuptake inhibitor: agent that acts to prevent the uptake of noradrenaline by neurons

Figure 3. Tapentadol ER Affects Ascending and Descending Pain Pathways[12,13]



Respiratory depression is a risk for all patients receiving opioid therapy. However, it is more likely to occur in elderly or debilitated patients, and in patients who suffer from conditions such as **asthma**, **chronic obstructive pulmonary disorder**, and **sleep apnea**, which can cause reduced oxygen levels and increased levels of CO_2. In these patients, moderate therapeutic doses may significantly decrease pulmonary ventilation.[14]

With repeated use of opioid drugs, **tolerance** to the respiratory depressant effects develops over time, and higher doses can be administered without adverse effects.[15] This is similar to how alcoholics can tolerate increasing amounts of alcohol over time.

asthma: episodic narrowing and inflammation of the airways that can by caused by a variety of stimuli

chronic obstructive pulmonary disorder (COPD): any of a group of debilitating, progressive, and potentially fatal lung diseases that can cause permanent or temporary narrowing of small bronchi and a slowed rate of forced expiratory flow

sleep apnea: temporary absence of breathing during sleep

tolerance: adaptation to a drug so that exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time

MISUSE, ABUSE, AND DIVERSION

Approximately 130 million people in the United States suffer from chronic pain,[10] or pain that lasts for 3 months or longer.[16] Opioid drug therapy is an option for pain management in this patient population.[10] However, because opioid medications are associated with a high risk of misuse, abuse, and diversion, the need to provide adequate pain relief for patients with chronic pain is coupled with a need to minimize the risk for the development of **aberrant drug-related behaviors**.[10]

aberrant drug-related behaviors: behaviors occurring outside the boundaries of an agreed upon treatment plan established early in the patient–doctor relationship[19]

Before we learn about the potential for misuse, abuse, and diversion of opioid drugs, let's take a closer look at what these terms mean.

Making the Link

Data from the National Survey on Drug Use and Health (NSDUH) show that in 2009, among individuals over 12 years of age, who were dependent on or abused illicit drugs, 1.9 million were diagnosed with dependence or abuse of pain relievers. Only dependence or abuse of marijuana was diagnosed in more individuals (4.3 million). Furthermore, the number of individuals with marijuana dependence or abuse has remained stable since 2002, while the number of individuals diagnosed with pain reliever dependence or abuse increased from 1.5 million.[17]

Misuse

Misuse is the use of a drug outside label directions or in a way other than prescribed or directed by a healthcare professional.[18] This includes, but is not limited to, abuse and diversion. For example, patients who develop tolerance to an opioid medication may take more medication than prescribed to achieve adequate pain relief; while these patients are misusing the medication, they are not abusing it, nor are they addicted.[19]

Abuse

Abuse is the nonmedical use of a drug, repeatedly, or even sporadically, for the positive psychoactive effects it produces.[18] Abuse of opioid medications is associated with a serious risk for overdose and drug-related fatalities resulting from respiratory depression.[20]

Individuals looking for opioid-induced euphoria may take a drug in ways it was not intended to be used to "get high." They may take an excess of medications orally; chew and swallow the pills; or crush the pills prior to taking orally, snorting, or reconstituting for injection.[10] They may manipulate sustained-release formulations to provide immediate release of a drug portion that was intended to be released over 12 to 24 hours, leading to an increased risk of serious adverse reactions.[19,21]

Diversion

Diversion refers to obtaining a drug that is prescribed for legal purposes for use in an illicit manner.[10] In most cases, diversion occurs when an individual with a prescription passes their drugs to family or friends. Abusers may also purchase prescription drugs from family members or friends, or steal them. Other methods in which drugs may be diverted include "doctor shopping" or obtaining multiple prescriptions from different physicians, usually by fabricating or exaggerating symptoms.[10,22]

Table 2. Misuse, Abuse, and Diversion

Term	Definition*	Risks	Example
Misuse	Use of a drug outside label directions, or in a way other than prescribed or directed by a healthcare professional[18]	Societal risks: increases in crime (including violent and property crimes) Individual risks: include addiction, overdose, death (usually due to respiratory depression)[20,22]	Offering prescribed medication to a friend/family member with similar symptoms[23]
Abuse	Nonmedical use of a drug for the positive psychoactive effects it produces[16]	Societal risks: increases in crime (including violent and property crimes) Individual risks: include addiction, overdose, death (usually due to respiratory depression)[20,22]	Continuing to take a medication after it is no longer medically necessary for the "high" it produces[23]
Diversion	The acquisition of a drug that is prescribed for legal purposes for use in an illicit manner[10]	Societal risks: increases in crime (including violent and property crimes) Individual risks: include addiction, overdose, death (usually due to respiratory depression)[20,22]	Illegal sale or recycling of prescriptions by physicians and pharmacists[22,24]

*These definitions are also provided in the glossary at the end of this Module.

Making the Link

Friends and relatives are the primary sources for prescription opioid drugs among most abusers.

Data from the National Survey of Drug Use and Health (NSDUH) found that in 2008-2009, more than half (55.3%) of the individuals 12 and older who used pain relievers for a nonmedical purpose, obtained the drug for free from a friend or family member. Another 9.9% of users bought them from a friend or family member, and 5% took them from a friend or relative without asking.[17]

The Risks of Misuse, Abuse, and Diversion of Opioid Drugs

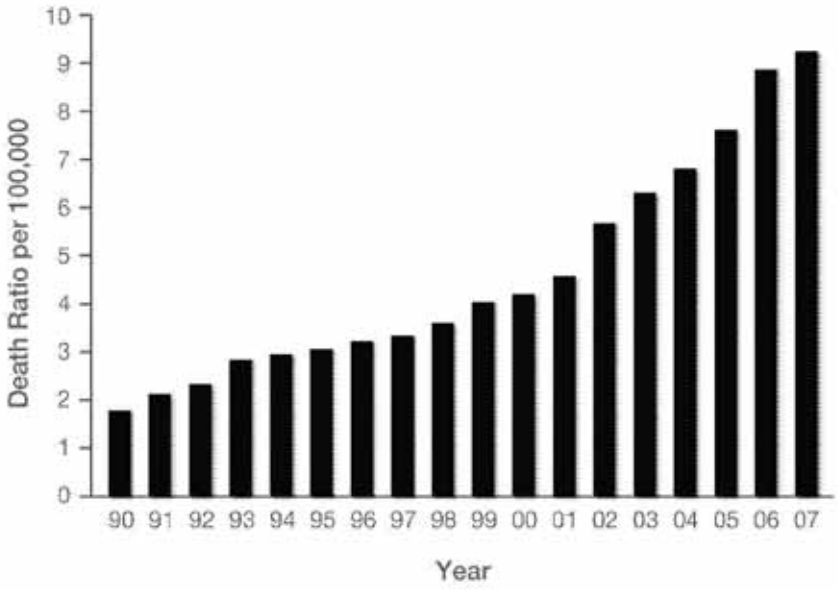
Opioids, including tapentadol, morphine, oxycodone, and hydromorphone-based products, are federal Drug Enforcement Administration (DEA) Schedule II substances. Schedule II drugs have an accepted medical use, but also have a high potential for abuse and the potential for psychologic or physical dependence.[21]

Schedule II products are subject to strict regulatory controls, which include product tracking, 100% accountability from the point of manufacture to the point of dispensing, and dispensing restrictions. Refills of these drugs are not permitted, although a prescriber may issue multiple prescriptions to some patients (allowing for a 90-day supply).[25] Schedule II drugs may be ordered orally only in an emergency situation.[25]

The regulatory controls and restrictions imposed by Schedule II designation serve as an important means of preventing the abuse and diversion of opioid drugs.[21] Despite the regulatory controls that are in place to prevent the misuse, abuse, and diversion of Schedule II drugs, data show that as the number of prescriptions for opioid drugs increases, so does the frequency of misuse, abuse, overdose, and drug-related fatalities.[20]

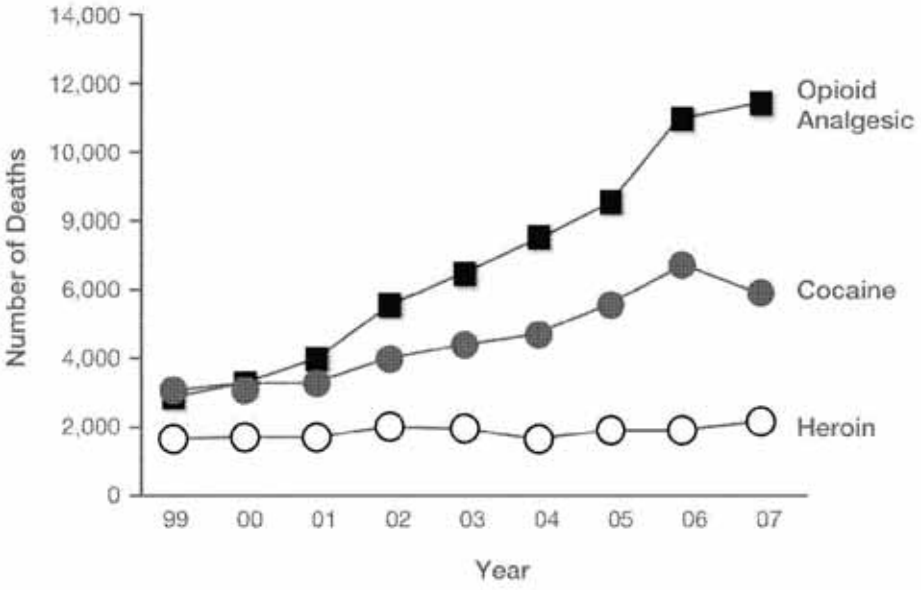
Data from the Centers for Disease Control and Prevention (CDC) show that the medical use of opioid painkillers has increased at least 10-fold over the last 20 years.[20] The rate of fatal drug overdoses has also increased—with rates approximately 5-fold higher in 2007 compared with those seen in 1990.[20]

Figure 4. Rate of Unintentional Drug Overdose Death in the United States, 1990-2007[20]



This increase in the drug overdose fatalities has been largely attributable to the misuse and abuse of prescription opioid drugs.[20] In 2007, cocaine, heroin, and prescription opioid drugs were the most common causes of drug-related deaths, and prescription opioids were responsible for more deaths than heroin and cocaine combined.[20]

Figure 5. Unintentional Drug Overdose Deaths by Major Type of Drug (United States, 1999–2007)[20]



The Relevance of Misuse, Abuse, and Diversion to Tapentadol ER

Tapentadol is a mu-opioid receptor agonist, and tapentadol ER is a Schedule II substance. Like other Schedule II opioid drugs, there is a risk for misuse, abuse, and diversion of tapentadol ER. *Therefore, tapentadol ER is subject to all of the regulatory restrictions associated with Schedule II classification.*[26] The same risks apply to NUCYNTA®.

Like other opioid drugs, the use of tapentadol ER by someone for whom it was not prescribed, or in a manner other than prescribed, can result in serious adverse effects, including death. Tapentadol ER should be taken exactly as prescribed by the healthcare professional. *Breaking, crushing, chewing, or dissolving tapentadol ER tablets before swallowing could result in overdose, leading to respiratory depression, and possibly death.*[14]

Tapentadol ER, like NUCYNTA®, should be kept in a childproof container and stored in a safe place to prevent theft of the medication. It is important to keep tapentadol ER away from children and other individuals for whom it is not prescribed. Accidental ingestion of tapentadol ER by a child is a medical emergency that can result in death.[14]

Opioid Tolerance in the Context of Addiction

It is important to understand that the use of opioid medications, even when taken as prescribed to treat a medical condition, may result in physical dependence and tolerance to the drug. However, physical dependence and tolerance should not be confused with addiction.[27]

The American Academy of Pain Medicine (AAPM), the American Pain Society (APS), and the American Society of Addiction Medicine (ASAM) have developed consensus definitions for addiction, physical dependence, and tolerance. These definitions are shown in Table 3 on the next page.[27]

Table 3. Definitions developed by the American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine[27]

Term	Definition*	Example
Addiction	A primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.	A 32-year-old woman with a history of substance abuse is prescribed opioids for the treatment of back pain; she frequently borrows medications from a family member, claiming she forgot or lost her medication; family and friends have noticed a negative change in her behavior and believe it is connected with the use of the medication[19]
Physical dependence	A state of adaptation that is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.	A 50-year-old man with metastasized colon cancer has been taking a long-acting opioid for several months; he normally gets his medication delivered to his home; this month's delivery did not arrive until after his medication ran out; as the levels of medication in his body dropped, he began to feel nauseous and sweat profusely; upon restarting his pain medication, symptoms abated[28]
Tolerance	A state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time.	A 68-year-old woman has been taking a stable dose of long-acting hydrocodone for 2 years to manage chronic low back pain; she asks her doctor to increase her pain medication, since the dose she has been taking is no longer effective[19]

*These definitions are also provided in the glossary at the end of this Module.

Most patients who receive prolonged opioid therapy will develop physical dependence, and some will develop tolerance. However, the majority of these patients do not develop addictive disorders.[27] The key distinction is that addiction refers to a maladaptive pattern of behavior, while physical dependence and tolerance are biologic changes that may be seen with both appropriate and inappropriate drug use.[27]

In patients who are physically dependent on opioids, a reduction of the level of opioids in the blood (eg, suddenly reducing the drug dosage or administering an opioid **antagonist**) may cause a wide variety of symptoms including anxiety; irritability; chills and hot flashes; sleep disturbances; nausea, vomiting and diarrhea; **lacrimation**; **rhinorrhea**; **diaphoresis**; and joint pain. However, once opioid treatment is no longer needed, patients are able to discontinue opioid use without difficulty, provided the dosage is **tapered** gradually.[28]

antagonist: a drug that neutralizes or counteracts the effects of another drug

lacrimation: the secretion or discharge of tears

rhinorrhea: runny nose

diaphoresis: profuse sweating

taper: in the context of opioid drugs, to decrease the dosage of an opioid gradually to avoid withdrawal symptoms

Predicting and Assessing Drug-Seeking Behavior

There are several strategies that healthcare providers can use to minimize the risks associated with the use of opioid medications. These strategies include risk assessment and stratification, and ongoing monitoring for signs of misuse.[19]

Risk Assessment

By assessing a patient's likelihood of misusing or abusing opioids prior to initiating opioid therapy, the healthcare provider can ensure that appropriate safeguards are included in the pain management plan.[19] Individuals being considered for opioid treatment should be assessed for known risk factors for opioid abuse, including smoking, psychiatric disorders, and personal or family history of substance abuse.[19]

There are numerous screening tests designed to help healthcare providers assess the patient's risk for misuse, abuse, or diversion of opioid medications, as well as screening tests to determine if a patient has a problem with drug or alcohol abuse.[19] Examples of screening tests that have been validated in clinical studies include the Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP®-R) and the Opioid Risk Tool (ORT). Both of these tests assess an individual's risk of misusing or abusing opioid medications. Other screening tests, such as the CAGE and CAGE Adapted to Include Drug (CAGE-AID) can be used to screen for alcoholism or drug abuse.[29]

Screening tests, such as the ones discussed over the next few pages, are intended to identify the likelihood that an individual will develop aberrant drug behaviors if opioid therapy is prescribed. They are not intended to be used to screen patients in or out of opioid therapy.[19] If opioid therapy is determined to be the best form of pain management for a patient at risk for misusing or abusing drugs—or for a person with an active substance abuse problem—opioid therapy can be initiated with a highly structured treatment and risk management plan in place.[19]

Screener and Opioid Assessment for Patients With Pain (SOAPP®)

Developed in 2003 with support from Endo Pharmaceuticals and the National Institute on Drug Abuse (NIDA), the SOAPP® tool is a 24-item questionnaire to help healthcare providers predict a patient's relative risk for developing problems if prescribed long-term opioid therapy.[30] Shorter versions (5 and 14 questions) of the SOAPP® are also available.[31] Healthcare providers can download all versions of the SOAPP® tool at www.painedu.org.[31]

The SOAPP®-R is the latest version of the screening tool. The 24-item questionnaire takes less than 10 minutes to complete and has been validated in 500 chronic pain patients.[30]

The questions included in the SOAPP®-R are shown in Table 4 on the next page.

Table 4. Screener and Opioid Assessment for Patients With Pain-Revised (SOAPP®-R)[32]

Question	Answer
1. How often do you have mood swings?	(Never, Seldom, Sometimes, Often, or Very Often)
2. How often have you felt a need for higher doses of medication to treat your pain?	
3. How often have you felt impatient with your doctors?	
4. How often have you felt that things are just too overwhelming that you can't handle them?	
5. How often is there tension in the home?	
6. How often have you counted pain pills to see how many are remaining?	
7. How often have you been concerned that people will judge you for taking pain medication?	
8. How often do you feel bored?	
9. How often have you taken more pain medication than you were supposed to?	
10. How often have you worried about being left alone?	
11. How often have you felt a craving for medication?	
12. How often have others expressed concern over your use of medication?	
13. How often have any of your close friends had a problem with alcohol or drugs?	
14. How often have others told you that you have a bad temper?	
15. How often have you felt consumed by the need to get pain medication?	
16. How often have you run out of pain medication early?	
17. How often have others kept you from getting what you deserve?	
18. How often, in your lifetime, have you had legal problems or been arrested?	
19. How often have you attended an AA or NA meeting?	
20. How often have you been in an argument that was so out of control that someone got hurt?	
21. How often have you been sexually abused?	
22. How often have others suggested that you have a drug or alcohol problem?	
23. How often have you had to borrow pain medications from your family?	
24. How often have you been treated for an alcohol or drug problem?	

Scoring: Never = 0 points; Seldom = 1 point; Sometimes = 2 points; Often = 3 points; and Very Often = 4 points

Score of 18+ = increased risk

The SOAPP®-R screening test should be used only with chronic pain patients who are being considered for long-term opioid therapy. It is not appropriate for use with all chronic pain patients.[32] Use of the SOAPP®[31]:

- May help the healthcare provider to better predict the likelihood that a patient will misuse or abuse opioids
- May help the provider determine the level of monitoring appropriate for a particular patient and document those decisions[31]

Opioid Risk Tool (ORT)

The Opioid Risk Tool (ORT) is a 5-question assessment that healthcare providers may use as an aid in predicting which patients are at risk of misusing or abusing opioid drugs based on known risk factors associated with abuse or addiction (see Table 5).[33]

Table 5. Opioid Risk Tool (Physician Form)[33]

Item	Mark Each Box That Applies	Item Score (Female)	Item Score (Male)
Family history of substance abuse			
Alcohol	[ ]	1	3
Illegal drugs	[ ]	2	3
Prescription drugs	[ ]	4	4
Personal history of substance abuse			
Alcohol	[ ]	3	3
Illegal drugs	[ ]	4	4
Prescription drugs	[ ]	5	5
Age (mark box if 16–45)	[ ]	1	1
History of preadolescent sexual abuse	[ ]	3	0
Psychological disease			
Attention deficit disorder (ADD), obsessive-compulsive disorder (OCD), bipolar, schizophrenia	[ ]	2	2
Depression	[ ]	1	1
Total*			

* Use the appropriate point total for each checked box and total up the points. Total score risk category:

Low risk: 0–3 points

Moderate risk: 4–7 points

High risk: ≥8 points

Based on the patient's score, they are assigned to 1 of 3 risk categories: high risk (likely to abuse opioids), moderate risk (equally likely to abuse or not abuse opioids), low risk (unlikely to abuse opioids).[33]

CAGE and CAGE Adapted to Include Drug (CAGE-AID)

The CAGE questionnaire is a simple four-question tool designed to help healthcare professionals detect alcoholism. The acronym CAGE is a mnemonic device that uses the first letter of the key word for each of the four questions to aid the healthcare professional in remembering the questions.[34] Although the CAGE was initially developed as a screening tool for alcoholism, a version of the assessment has been developed to detect both alcoholism and drug abuse (CAGE-AID).[29] See Table 6.

Table 6. The CAGE and CAGE-AID Questionnaires[35]

	Questions
C	Have you ever felt you ought to **Cut** down on your drinking *or drug use*?
A	Have people **Annoyed** you by criticizing your drinking *or drug use*?
G	Have you felt bad or **Guilty** about your drinking *or drug use*?
E	Have you ever had a drink *or used drugs* first thing in the morning to steady your nerves or to get rid of a hangover (**Eye-opener**)?

Note: The plain text represents the original CAGE questions. Italicized text indicates text that was added to produce the CAGE-AID.

CLASS-WIDE RISK EVALUATION AND MITIGATION STRATEGIES (REMS) LABELING FOR OPIOID MEDICATIONS

Opioid therapy is important for the management of patients with chronic pain that does not respond to other types of pain management therapies. However, it is necessary to balance the need for adequate pain relief for appropriate patients with the need to prevent misuse, abuse, and diversion of opioid medications.[10] The misuse and abuse of opioid drug products, in particular the long-acting and extended-release formulations of these products, has resulted in a widespread and serious public health crisis of addiction, overdose, and drug-related deaths.[21]

In 2009, the FDA announced plans to require REMS for all long-acting and extended-release opioid medications.[21] In April 2011, the FDA announced the elements of the class-wide REMS, which will require manufacturers of long-acting and extended-release opioids to ensure that training is provided to all healthcare professionals who prescribe these medications.[36]

The class-wide REMS is necessary for "certain long-acting and extended-release opioid products, including tapentadol ER, to ensure that the benefits of the drug continue to outweigh the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse."[37] The FDA has limited the class-wide REMS to long-acting and extended-release formulations because data indicate these formulations bear greater risk than immediate-release opioids.[21] Table 7 lists the elements required by the class-wide REMS.

Table 7. Elements of the Class-wide REMS for Opioids[37]

Medication Guides	
• Language regarding the safe use of all opioid drug products • Product-specific information	
Elements to Assure Safe Use (ETASU)	
Prescriber Education	• Drug sponsor must inform prescribers of REMS program and need to successfully complete training[37] • Education program will provide information on how to[36]: – Weight risks and benefits of opioid therapy – Choose patients appropriately – Manage and monitor patients – Counsel patients on the safe use of these drugs – Recognize evidence of and potential for opioid misuse, abuse and addiction • Must include knowledge assessment and proof of program completion[37] • Prescriber participation not mandatory[36]
Patient Education[37]	• Manufacturer to develop materials to provide to patients: – Proper use of opioid medications – Risks associated with opioid drugs – List of websites that provide additional information
Implementation and Assessments of Class-wide REMS	
• Implementation of a single shared platform – Education programs[36] – Consortium of impacted companies* – Most elements will be common[38] – Each product will have its own medication guide distributed by company[38]	

* An industry consortium of 25 companies that manufacture long-acting and extended-release opioid medications formed in 2009, when the FDA announced its intention to require a class-wide REMS.[39]

Manufacturers of long-acting and extended-release opioid medications are now expected to work together to provide the educational materials as part of a class-wide single, shared system.[36] Although the FDA has required that sponsors of individual long-acting and extended-release opioid drugs submit a REMS proposal within 120 days of the REMS announcement, the contents of these proposals are expected to be largely identical. The Medication Guides are expected to be the only product-specific documents[38]; however, FDA is developing a model Medication Guide that will include the content common to all long-acting and extended-release opioids and that will indicate where the product-specific information should be added.[38]

Development and implementation of the education program is expected to be complete in early 2012.[40] Until the development and implementation of the class-wide REMS is complete, long-acting and extended-release opioids will continue to be approved and marketed under interim REMS.[40] These REMS are not standardized.

FDA-Approved REMS Programs for Competitive Products

As mentioned previously, the FDA announced plans to develop a class-wide REMS in 2009.

Pending development of the program, long-acting and extended-released opioid drugs, some of which already have risk management programs in place, continue to be marketed under the approved labeling.[41] The FDA also approved new drug applications in this class with an "interim" REMS. In this next section, we will look at the current FDA-approved REMS for three long-acting or extended-release products that were approved after the FDA announced plans for a class-wide REMS.[42]

The REMS for OxyContin®, Exalgo®, and Embeda® share the same goals[43,44,45]:

1. To inform patients and healthcare professionals about the potential for abuse, misuse, overdose, and addiction of OxyContin®, or Embeda®, or Exalgo®
2. To inform patients and healthcare professionals about the safe use of OxyContin®, or Embeda®, or Exalgo®

Table 8 (see next page) shows the components of the interim REMS for each product.

Risk Management (REMS) for Tapentadol ER

Table 8. Components of the Interim REMS for OxyContin®, Exalgo®, and Embeda®[43,44,45]

Drug Name Component Drug(s) Drug Company (year approved)	Timetable for Assessment*	MG	Communication Plan	ETASU	Implementation Plan
OxyContin® Oxycodone hydrochloride CR Purdue Pharma L.P. (2010)[43]	✓	✓		✓	Not required[43]
Embeda® morphine sulfate and naltrexone hydrochloride King Pharmaceuticals (2009)[44]	✓	✓	✓		Not required[44]
Exalgo® hydromorphone hydrochloride Mallinckrodt Inc (2010)[44]	✓	✓		✓	Not required[44]

MG = Medication Guide

ETASU = Elements to Assure Safe Use

* The Embeda® REMS requires assessment of the REMS 6 months and 1 year after the approval date of the NDA and annually thereafter. The REMS for Exalgo® and OxyContin® require assessment of the REMS every 6 months from the date of approval of the REMS for the first year, and annual assessments thereafter.

CR = controlled release

XR = extended release

All 3 products include a Medication Guide as 1 of the elements to support the goals of the REMS.[43,44,45] The medication guides are part of the package insert, located in the last section. They are also distributed as stand-alone documents.

The pharmacist is required to include a Medication Guide with every dispensed prescription of OxyContin®, Embeda®, or Exalgo®. In addition, the Medication Guides for all 3 products can be obtained through the product's website, or by calling a toll-free number.[43,44,45]

Timetables for Assessment of the REMS are a required component of all REMS.[2] The REMS for Embeda® required an assessment 6 months and 1 year following the approval date of the new drug application (NDA), and annually thereafter. For OxyContin®, and Exalgo®, a REMS assessment was required 6 months and 1 year following approval of the REMS, and an annual assessment was required thereafter.[43,44,45]

The interim REMS for Embeda® includes a Communication Plan, which requires King Pharmaceuticals to send letters to healthcare professionals, professional societies, and state medical and pharmacy boards.[44] The REMS for Exalgo® and OxyContin® both include ETASUs that require the drug sponsors, (Mallinckrodt Inc and Purdue Pharma L.P., respectively) to make educational training available to prescribers of the drug, and to send a letter to prescribers informing them of the REMS and the need to complete the educational program.[43,45]

The information disseminated to prescribers through the Communication Plan for Embeda® and through the educational programs of OxyContin® and Exalgo® programs is similar, and includes guidance on: proper patient selection, dosing, the risk of opioid abuse, identification of patients with increased likelihood of abuse, product-specific risks, proper storage of opioid medications, and the need to provide and explain the Medication Guide to patients.[43,44,45]

While prescriber participation in the educational programs is voluntary,[43,45] healthcare professionals participating in the education programs for Exalgo® and OxyContin® are asked to fill out a form that certifies they have completed the training. They are also asked to complete a test that assesses their knowledge of the educational material. Mallinckrodt Inc and Purdue Pharma L.P. are required to maintain a list of those prescribers who have completed the training.[43,45]

Making the Link
The proposed REMS for tapentadol ER is modeled after the REMS for Exalgo®.

THE RIGHT PATIENT, THE RIGHT DOSE

As you have learned, opioid drugs are a vital component of pain management programs, but they are also associated with significant risks.[10] An integral part of the risk management for opioid drugs is ensuring that the prescribed treatment and the prescribed dose are appropriate for each individual patient.

Some opioid drugs are indicated only for patients who are already opioid tolerant, while others may be appropriate for individuals who are not opioid tolerant or who have not taken opioid medications before.[43,45]

To decrease the risk of opioid-related adverse effects such as respiratory depression, patients who are opioid-naïve, or who have only modest previous opioid exposure, should initiate opioid treatment at a low dose and increase the dosage slowly.[16] Prescribing Information for opioid medications often include recommended dosages for patients who are opioid-naïve.

Making the Link
Because of the risks associated with opioid medications, it is important to prescribe these medications only to appropriate patients, and only at appropriate doses. Each patient should receive a risk-benefits evaluation to ensure that improvements in patient pain and functioning outweigh the risks of misuse, abuse, and addiction that are associated with opioid drug therapy.[16]

Key Points

- Risk Evaluation and Mitigation Strategies (REMS) are FDA-mandated risk management programs that may be required for any drug, pre- or postmarketing, to ensure the benefits of the drug outweigh the risks associated with its use.[1]
- All REMS include a timetable for assessment of the REMS, and may also include a Medication Guide, a Communication Plan, Elements to Assure Safe Use (ETASU), and an Implementation Plan (for some ETASUs).[2]
- Treatment with opioid medications can cause drug-induced inhibition of the opioid receptors in respiratory control centers, resulting in respiratory depression. While respiratory depression does not often occur with the use of opioid medications, it is potentially a fatal adverse effect, and one of the most serious risks associated with opioid use.[9]
- Opioid medications are associated with a risk for misuse, abuse, and diversion; therefore, the need to provide adequate pain relief for patients with chronic pain is coupled with a need to minimize the risk for the development of aberrant drug-related behaviors.[10]
- Individuals looking for opioid-induced euphoria may take a drug in ways it was not intended to be used to "get high." They may take an excess of medications orally; chew and swallow the pills; or crush the pills prior to taking orally, snorting, or reconstituting for injection. This misuse of prescription opioid drugs is responsible for a significant increase in drug overdose fatalities.[10,20]
- Tapentadol ER is a Schedule II drug, and like other drugs of that class, has a high risk of being misused or abused. It is important to keep tapentadol ER out of the reach of children or other individuals for whom it is not prescribed.[14,26]
- The use of opioid medications is associated with the development of physical dependence and drug tolerance. These are expected consequences of treatment with opioid medications, and should not be confused with addiction, which is characterized by maladaptive behaviors such as compulsive use, continued use despite harm, and craving.[27]
- Prior to initiating therapy with opioids, the patient's risk for developing aberrant drug behaviors should be assessed. Screening tests such as the SOAPP®, ORT®, and CAGE questionnaire can help the healthcare provider determine what safeguards are appropriate for each patient's risk management plan.[19]

Risk Management (REMS) for Tapentadol ER

Key Points (continued)

- In April 2011, the FDA announced the elements of a class-wide REMS, deemed necessary for "certain long-acting and extended-release opioid products, including tapentadol ER, to ensure that the benefits of the drug continue to outweigh the risks."[36]
- Development and implementation of the education program is expected to be complete in early 2012. Until the development and implementation of the class-wide REMS is complete, long-acting and extended-release opioids will continue to be approved and marketed under interim REMS.[40]
- The REMS for OxyContin®, Embeda®, and Exalgo® have common goals[43,44,45]:
  - To inform patients and healthcare professionals about the potential for abuse, misuse, overdose, and addiction of OxyContin®, or Embeda®, or Exalgo®
  - To inform patients and healthcare professionals about the safe use of OxyContin®, or Embeda®, or Exalgo®
- To support the goals of the REMS, OxyContin®, Embeda®, and Exalgo® all require that a Medication Guide is dispensed with all filled prescriptions. In addition, both OxyContin® and Exalgo® require ETASUs (training for prescribers), while the Embeda® REMS includes a Communication Plan.[43,44,45]

REVIEW ONE

A. Opioids cause respiratory depression by inhibition of mu-opioid receptors in the respiratory centers of the:

_____ 1. lungs.

_____ 2. brainstem.

_____ 3. respiratory muscles.

_____ 4. opioid receptors.

B. Misuse of an opioid drug is:

_____ 1. always indicative of substance abuse and addiction.

_____ 2. the nonmedical use of a drug, repeatedly, or even sporadically, for the positive psychoactive effect it produces.

_____ 3. the use of a drug outside label directions or in a way other than prescribed by a healthcare professional.

_____ 4. the use of a drug prescribed for legal purposes for use in an illicit manner.

C. Which of the following is the most common form of diversion of opioid drugs?

_____ 1. individual with prescription gives drugs to family or friends

_____ 2. theft of the medication from pharmacies

_____ 3. purchase of drug from family, friend, or drug dealer

_____ 4. doctor shopping

D. The rates of fatal opioid drug overdoses were approximately _____ higher in 2007 compared to those seen in 1990.

_____ 1. 3-fold

_____ 2. 5-fold

_____ 3. 7-fold

_____ 4. 10-fold

E. Most patients who receive prolonged opioid therapy will develop:

_____ 1. drug-related aberrant behaviors.

_____ 2. drug addiction.

_____ 3. physical dependence.

_____ 4. all of the above.

F. Tapentadol, morphine, oxycodone, and hydromorphone-based products are:

_____ 1. Schedule I drugs.

_____ 2. Schedule II drugs.

_____ 3. Schedule III drugs.

_____ 4. Schedule IV drugs.

G. The FDA has announced a class-wide REMS for long-acting and extended-release opioid drugs because the misuse and abuse of these products has resulted in a widespread and serious public health crisis of:

_____ 1. opioid addiction.

_____ 2. opioid overdose.

_____ 3. deaths resulting from opioid overdose.

_____ 4. all of the above.

H. Patients who score between 4 and 7 points on the Opioid Risk Tool (ORT):

_____ 1. are at low risk of abusing opioid drugs.

_____ 2. have a moderate risk of abusing opioid drugs.

_____ 3. have a high risk of abusing opioid drugs.

_____ 4. should not receive treatment with opioid drugs.

I. The interim REMS for OxyContin® includes all of the following elements EXCEPT:

_____ 1. timetable for assessment of the REMS.

_____ 2. Medication Guide.

_____ 3. Elements to Assure Safe Use (ETASU).

_____ 4. Implementation Plan.

J. The interim REMS for _____ includes a communication plan.

_____ 1. Embeda®

_____ 2. Tapentadol ER

_____ 3. Exalgo®

_____ 4. OxyContin®

(Answers are on page 30.)

Review One Answers

A. 2
B. 3
C. 1
D. 2
E. 3
F. 2
G. 4
H. 2
I. 4
J. 1

GLOSSARY

aberrant drug-related behaviors: behaviors occurring outside the boundaries of an agreed upon treatment plan established early in the patient–doctor relationship[16]

abuse: nonmedical use of a drug for the positive psychoactive effects it produces[18]

addiction: a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations; it is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving[27]

agonist: a drug that binds a receptor and stimulates its function[46]

antagonist: a drug that neutralizes or counteracts the effects of another drug[46]

asthma: episodic narrowing and inflammation of the airways that can by caused by a variety of stimuli[46]

brainstem: the stem-like part of the brain that connects the cerebral hemispheres with the spinal cord; it comprises the medulla oblongata, the pons, and the midbrain[46]

chemoreceptor: a receptor that is activated by chemical substances[46]

chronic obstructive pulmonary disorder (COPD): any of a group of debilitating, progressive, and potentially fatal lung diseases that can cause permanent or temporary narrowing of small bronchi and a slowed rate of forced expiratory flow[46]

diaphoresis: profuse sweating[46]

diaphragm: the thin muscle that separates the chest from the abdomen, and contracts and relaxes during breathing[46]

diversion: the acquisition of a drug that is prescribed for legal purposes for use in an illicit manner[10]

intercostal muscles: muscles between the ribs that contract during inspiration[46]

lacrimation: the secretion or discharge of tears[46]

medulla: a portion of the brainstem that contains nerve centers vital to life that govern breathing, the action of the heart, and swallowing[46]

misuse: use of a drug outside label directions, or in a way other than prescribed or directed by a healthcare professional[18]

mu-opioid receptors: receptors responsible for initiating a signaling cascade that mediates the actions of many hormones and neurotransmitters[9]

noradrenaline reuptake inhibitor: agent that acts to prevent the uptake of noradrenaline by neurons[46,47]

opioid: a term originally used to denote synthetic narcotics resembling opiates but increasingly used to refer to both opiates and synthetic narcotics[47]

physical dependence: a state of adaptation that is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist[27]

respiratory depression: ventilation that fails to provide adequate oxygen to the cells and to remove excess carbon dioxide from them[46]

rhinorrhea: runny nose[46]

sleep apnea: temporary absence of breathing during sleep[46]

taper: in the context of opioid drugs, to decrease the dosage of an opioid gradually to avoid withdrawal symptoms[44]

tolerance: adaptation to a drug so that exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time[27]

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